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AT A GLANCE

(ARCHIVED) Mechanisms for Increased Transmission of SARS-CoV-2 Variants of Concern

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Background

Public Health Ontario (PHO) has reviewed and continues to monitor evidence regarding the four severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants of concern (VOCs) that have been detected in Ontario: Pango lineage B.1.1.7 (Alpha),[1] B.1.351 (Beta),[2] P.1 (Gamma)[3] and B.1.617.2 (Delta).[4] Recent estimated proportions of VOC cases based on mutation profiles from June 22, 2021 to June 28, 2021 in Ontario indicated that the majority of circulating VOC was Delta (56.5%), followed by Alpha (35.1%), other mutations (6.0%), and Gamma and Beta (2.4%).[5,6]

These four VOCs have been identified to have significantly increased reproduction numbers compared to non-VOC strains of SARS-CoV-2,[7] raising questions about whether these mutations affect the mode of transmission (e.g., whether there is a shift to increased fitness for long-range aerosol transmission). Modes of transmission were previously reviewed in What We Know So Far publications,[8,9] but did not address how mutations may impact modes of transmission. To this end, a rapid literature search was conducted to obtain recent research articles (published and preprints) related to mechanisms for increased transmission of VOCs. Reviews were prioritized and primary articles were included where titles and abstracts specifically addressed modes of transmission.

Evidence on Mechanisms of Increased Transmissibility of VOCs

The impact of mutations seen in different VOC strains has been covered in recent reviews and includes increased binding affinity of the spike protein to host angiotensin-converting enzyme 2 (ACE2) receptor,[10-13] evasion of neutralizing antibodies,[10,11,13] increased viral loads,[12] and increased duration of shedding.[12]

For example, Alpha contains mutations that are potentially related to binding affinity to ACE2 receptor (N501Y), immune evasion (possibly directly or indirectly related to the spike deletion at position 69-70) and viral fusion (P681H).[1,10,13-15] Beta carries some of the same mutations as Alpha, but also contains mutations E484K and K417N that reduce binding of some antibodies.[10,11] K417N and K417T mutations have been reported to reduce ACE2 receptor affinity; however, when combined with the N501Y mutation have an overall net increase of ACE2 receptor affinity compared to non-VOC strains.[12] Gamma also harbours E484K and N501Y and thus has an increase in ACE2 receptor affinity, as well as the potential for immune evasion (particularly of therapeutic antibodies).[12] Despite the potential for immune escape, neutralization by antibodies from prior infection or vaccination remains largely effective and no significant increase in reinfection rates have been reported for VOCs in general.[11,16]

Antibodies produced from infection from one strain may not provide effective protection against other strains due to asymmetric heterotypic immunity.[12] Immune escape by Beta appears to be a concern for individuals previously infected by other strains and vaccinated individuals; however, convalescent sera from individuals infected with Beta shows high cross-reactivity to other VOCs.[12] There are similar concerns regarding reinfection by Gamma due to immune escape.[1,12,17] Most studies on transmissibility of VOCs have not been conducted in populations with high vaccination rates or high rates of natural immunity. The degree and impact of vaccine breakthrough/escape from natural immunity will become more apparent as larger proportions of populations are vaccinated, or from regions with highly impacted populations, and the transmission of VOCs continues to be studied in these populations. However, real world vaccine effectiveness data from Ontario have so far demonstrated very high vaccine effectiveness against SARS-CoV-2 including E484K-positive VOCs from a completed series of mRNA vaccines.[16]

Disease severity for Alpha is likely higher based on a meta-analysis of data from Ontario, the United Kingdom (UK) and Denmark. The data included all VOCs; however, Alpha was the predominant circulating VOC, and analyses showed a 63% higher risk of hospitalization (RR 1.63, 95% CI 1.44 to 1.83), a doubling of the risk of intensive care unit admission (RR 2.03, 95% CI 1.69 to 2.45), and a 56% higher risk of all-cause death (RR 1.56, 95% CI 1.30 to 1.87).[1,18] Disease severity may be higher for Beta, but data is confounded by the lack of hospital resources and differing demographics.[12] It is not entirely clear what role disease severity has on transmission; however, a higher viral load is associated with more severe disease and increased transmission risk.[19-21] Reports have been conflicting regarding increased viral loads and longer period of shedding for Alpha.[1,12,17,22]

Public Health England has published a brief one-page table (June 10, 2021) that is updated frequently as it relates to Delta transmission, disease severity and immunity.[23] Their current assessment suggests replication advantages based on *in vitro* data, possibly increased disease severity and immune evasion, which are similar mechanisms as Alpha for which there is more published literature. However, the brief suggests that Delta is more transmissible than B.1.1.7 and Public Health England's Technical Briefing 15 confirms that Delta is the dominant circulating VOC at this time.[24] A preprint has reported on the P681R mutation present in Delta, similar to the P681H mutation in Alpha, as likely conferring increased viral

fusion based on a fusion assay performed using D614G/P681R transfected HEK293 cells, compared to D614G transfected HEK293 cells.[25] Other mutations include D614G (associated with higher viral load), G142D (associated with immune evasion), L452R (associated with immune evasion and ACE2 binding affinity), T478K (associated with ACE2 binding affinity), and other mutations in the spike protein (D950N, T19R, Δ157/158).[1,26]

Evidence on the Impact of VOCs on Transmission Routes

Two studies were identified: one relating to aerosol stability (i.e., long-range aerosol transmission), the other to surface stability (i.e., fomite transmission).

Schuit et al. (2021) compared the stability in aerosols of a SARS-CoV-2 isolate (hCoV-19/USA/CA_CDC_5574/2020) containing all genomic mutations characteristic of Alpha to other SARS-CoV-2 isolates, including an isolate collected on January 19, 2020 (hCoV-19/USA/WA-1/2020).[27] Environmental conditions related to temperature (10, 20, 30 and 40 degrees Celsius [°C]), relative humidity (20, 37, 45, 53, 55, and 70%), and simulated sunlight (varying intensities and darkness) were modified. Isolate decay constants for infectivity ($k_{infectivity}$) were calculated using data from cell cultures. Although the stability of Alpha was higher at 20°C and 20% relative humidity in simulated sunlight ($k_{infectivity}$ = 0.209 ± 0.063 min^{-1}) compared to two other strains, the difference was small ($k_{infectivity}$ = 0.299 ± 0.047 min^{-1} and 0.312 ± 0.051 min^{-1}). This was effectively a difference of 11 minutes versus seven to eight minutes for 90% loss of infectivity. Further, the Alpha was no more stable than an early reference strain (hCoV-19/USA/WA-1/2020, $k_{infectivity}$ = 0.216 ± 0.056 min^{-1}). The authors concluded that it is unlikely that the transmissibility of the Alpha is associated with enhanced survival in aerosols.

Meister et al. (2021) investigated surface stability and surface disinfection profiles of Alpha and Beta compared to a reference wild type strain (B1.1.70).[28] Viability was determined by end-point-dilution assay on Vero E6 cells. There was no difference in susceptibility to heat (56°C), soap and ethanol treatment of VOC strains compared to reference strains using different concentrations and exposure times. Similar surface stability was reported for steel, silver, copper, surgical masks and respirators. The authors concluded that current recommendations for environmental cleaning still apply for Alpha and Beta. Their results indicated that there is no increased risk of fomite transmission due to VOC strains compared to a reference wild type strain.

Conclusion

Current reviews and select studies indicate that some mutations associated with VOCs act on the host-virus interaction and contribute to increased overall transmissibility of the variant. Two studies examining the modes of transmission found no clinically important differences between VOCs and wild type. Currently there is very little data related to mechanisms for increased transmissibility with respect to Beta, Gamma, and Delta. What little transmissibility data exists relates to ACE2 binding and immune evasion.[17] Reviews on this topic rapidly become out of date and new variants continue to be identified as variants of interest, some of which may become classified as VOCs in the future.[29] The significant transmissibility advantage of Delta versus Alpha warrants close attention to the data elucidating mechanisms of transmission of Delta.

A key limitation of this review is that it did not endeavour to be an exhaustive literature search and not all mutations and potential effects were reviewed, such as those that pertain to additional molecular-level host-virus interactions.

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